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We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade

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Running title: Simplifying HCV models of care

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Abstract

Globally, some 71 million people are chronically infected with hepatitis C virus (HCV). Marginalised populations, particularly people who inject drugs (PWID), have low testing, linkage-to-care and treatment rates for HCV. Several models of care (MoCs) and service delivery interventions have the potential to improve outcomes across the HCV cascade of care, but much of the relevant research was carried out when interferon-based treatment was the standard of care. Often it was not practical to scale up these earlier models and interventions because the clinical care needs of patients taking interferon-based regimens imposed too much of a financial and human resource burden on health systems. Despite the adoption of highly effective, all-oral direct-acting antiviral (DAA) therapies in recent years, approaches to HCV testing and treatment have evolved slowly and often remain rooted in earlier paradigms. The effectiveness of DAAs allows for simpler approaches and has encouraged countries where the drugs are widely available to set their sights on the ambitious World Health Organization (WHO) HCV elimination targets. Since a large proportion of chronically HCV-infected people are not currently accessing treatment, there is an urgent need to identify and implement existing simplified MoCs that speak to specific populations' needs. This article aims to: 1) review the evidence on MoCs for HCV; and 2) distil the findings into recommendations for how stakeholders can simplify the path taken by chronically HCV-infected individuals from testing to cure and subsequent care and monitoring.

Keywords: health systems, hepatitis C, models of care, people who inject drugs

Introduction

Viral hepatitis is a leading cause of mortality globally, with the hepatitis C virus (HCV) responsible for an estimated 350,000 deaths and 9.7 million disability-adjusted life years in 2016. [1] The World Health Organization (WHO) estimates that 80% of the people living with HCV have not been diagnosed. [2] Although HCV became a highly curable disease with the introduction of all-oral direct-acting antiviral agents (DAAs) in 2013, most countries have been slow to provide unrestricted access to these life-saving drugs [3] [4] and thus decrease the disease's spread [5] and reduce its prevalence.

Given the gravity of the epidemic and the effectiveness of the cure, in 2016 WHO made the elimination of viral hepatitis as a public health threat by 2030 the overriding goal of its first global health sector strategy on viral hepatitis. [6] The strategy stresses equity and leaving no affected populations behind in its ambitious targets of achieving an 80% reduction in HCV incidence and a 65% reduction in HCV mortality by 2030, as exemplified in its prevention target to increase the average number of sterile needles and syringes distributed to people who inject drugs (PWID) from 20 to 300 annually. Today, the unsafe injection of illicit drugs is a main driver of the global HCV epidemic. [2,7] It is estimated that 15.6 million people injected drugs globally in 2015, [8] and that 6.1 million of them were living with HCV. [9] Globally, if the risk of HCV transmission associated with sharing unsafe injecting equipment among people who currently inject drugs was removed, 43% of incident HCV cases would be prevented between 2018 and 2030. [10]

Evidence shows that in many settings, a relatively modest increase in treatment rates can enable a country that already provides good access to DAAs to achieve the WHO strategy's targets. A 2017 study modelling the HCV epidemic in Switzerland concluded that an annual treatment uptake of 10% would eliminate the disease by 2030 in PWID. [11] A second study made comparable projections for other European countries, but also found that some countries would need to scale up opioid substitution therapy (OST) and needle and syringe exchange programmes (NSP) interventions to reduce chronic HCV prevalence. [12] Yet in most countries of the world, particularly low and middle-income countries, access to DAAs and harm reduction services remains extremely limited, [13-15] and achieving the WHO targets will require major expansion of both forms of access. [16] That is because besides DAA therapy, which enables a sustained virologic response (SVR), the most effective form of HCV prevention for PWID is harm reduction, including opioid substitution therapy OST, NSPs, and supervised injecting centres.

In reality, global elimination of HCV will require major increases in services for all affected populations along the entire cascade of care, including testing, linkage to care, retention in care, treatment, chronic care and prevention of primary infection and reinfection.

The model of care (MoC): a tool for increasing treatment coverage

In 2013, Bruggmann and Litwin found that, while HCV treatment had been successfully delivered to many people, through various multidisciplinary models, few treatment settings were adapted to the needs of PWID. [17] PWID who have been treated, e.g. with OST, are often those who are most motivated to seek out health services, while those who are more marginalised find access difficult.

What is needed is a *model of care* (MoC) for each setting that specifically targets PWID and other marginalised high-burden populations, such as migrants or the homeless, while taking advantage of the characteristics of DAA therapy.

In this review, we use MoC to signify a setting-specific framework that outlines how to provide the relevant services and interventions throughout the HCV cascade of care. An MoC should address four key questions: *where* to provide the services, *what* services to provide, *who* to provide them and *how* to integrate them.

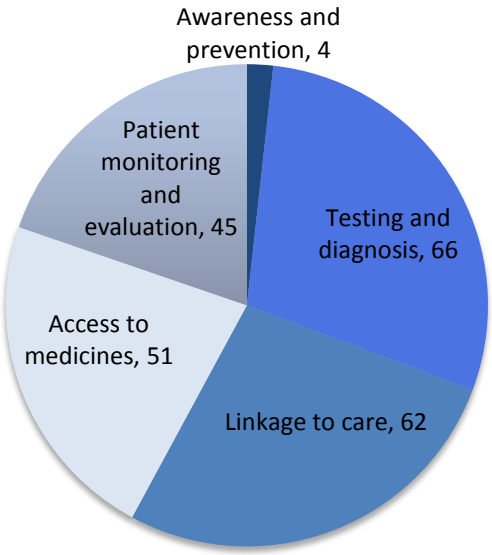
Box/Panel 1. Selection of new models of hepatitis C care presented in this review

- **Nurse-led**
- **Telemedicine**
- **Multidisciplinary (including non-medical personnel in the core team, e.g. social workers, case managers or psychologists)**
- **Pharmacist-led**
- **Mobile van units**

The models of HCV care were selected by reviewing the peer-reviewed literature in PubMed/Medline since 2014, references from relevant articles, and abstracts from the The Liver Meeting of the American Association for the Study of Liver Diseases (AASLD 2018); European Association for the Study of the Liver International Liver Congress (EASL ILC 2018 and 2019), and the International Network on Hepatitis in Substance Users (2018) by three independent researchers (CP, JC, EMR), who identified 71 studies that reported studies of new models of care to address HCV that had measurable outcomes. Table 1 presents selected case studies by country and population addressed, Table 2 highlights the main populations addressed, Table 3 describes setting, and Table 4 categorizes the provider type. Fig. 1 presents the stages of the cascade of care addressed (awareness and prevention, testing and diagnosis, linkage to care, access to medicine, and patient monitoring and evaluation) while Supplementary Table 1 summarizes measurable outcomes, including SVR where available. The search words were:

- PubMed search string (HCV[All Fields] OR ("hepatitis c"[MeSH Terms] OR "hepatitis c"[All Fields] OR "hepacivirus"[MeSH Terms] OR "hepacivirus"[All Fields])) AND model[All Fields] AND s[All Fields] AND care[All Fields]
- Conference abstract search using keywords “models of care”, “hepatitis C”, “HCV”, “public health”

Figure 1. Summary of articles included (n=71) classified by the stages in the cascade of care



One of the hallmarks of a good MoC is simplicity. Simplicity is key to the scaling up of interventions and widely considered a predictor of its success. [18-21] Fortunately, because DAAs have few side-effects and can be administered orally, MoCs designed to optimise DAA delivery are much simpler than those designed for pegylated interferon treatment, which required more pre-treatment diagnostic procedures (e.g pre-treatment liver biopsy, HCV genotyping) to exclude other causes of liver disease, as well as intensive monitoring and dose modification. Other elements that contribute to simplicity include effective linkage to care and the targeting and integration (e.g. co-location) of services. [22]

Targeting is also essential. It begins with a concerted effort to test members of hard-to-reach at-risk populations, using outreach to come in contact with them where they are, instead of waiting for them to present at healthcare facilities. Table 2 presents the seven main populations addressed by MoC studies from the DAA era. Of the 71 studies that we reviewed for this paper, 42 targeted PWID.

Among PWID and other vulnerable populations, rapid testing has been shown to substantially increase coverage and referral rates. [23-25] To date, many services have not been developed for vulnerable populations such as the homeless, PWID and prisoners, which must both contend with numerous social determinants [26-29] that contribute to poor quality of life and poor social functioning [30-31] as well as health inequalities. [32] It should be emphasised that HCV treatment should be offered based on clinical rather than social factors or injecting-related behaviours,[33-34] underlining the necessity of overcoming obstacles to HCV treatment delivery to PWID. In particular, several studies demonstrate that HCV treatment achieves acceptable outcomes in active injectors, and outcomes that are just as good in people on OST as in people who do not inject drugs. [35-37] An enabling policy environment is paramount, [38] since restrictive drug policies and the criminalisation of drug use not only drive much of the HCV epidemic among PWID [39] but also

discourage PWID from accessing both HCV services and drug treatment services, [40] while harm reduction services can offer HCV testing that many PWID would otherwise not access. At the same time, the daily support typically provided to OST clients on HCV treatment might also prove beneficial to other vulnerable individuals receiving treatment.

Perhaps the biggest obstacle to the scale-up of HCV services in many settings is affordability and availability, for both diagnostic tools and treatment. While the right to health suggests that anyone infected with HCV should have access to treatment, irrespective of disease stage and drug use, [41] some people must pay for them out of pocket in those countries where high costs and/or discrimination have led to reimbursement restrictions. Most countries that subsidise DAA therapy have restricted access in terms of who can prescribe and disease severity, [3] despite evidence that treatment is cost-effective when the long-term costs of morbidity, mortality and onward transmission are included in the calculations, and provided that harm reduction is widely available. [35, 42-47] Strategies that have proven successful in bringing DAA costs down to a fraction of the list price include directly negotiating with pharmaceutical companies, licensing generics and committing to scaling up treatment in order to secure bulk discounts and achieve economies of scale.[48]

Other obstacles also need to be overcome to scale up HCV treatment. [49-50] They include the heterogeneity of national policies,[51-53] a lack of appropriate infrastructure for HCV services in tertiary centres and addiction clinics, [17, 54-57] stigma and discrimination [58-59] (including the reluctance of some physicians to treat PWID [60-62], limited access to point of care diagnostics [63], and inadequate knowledge of HCV and HCV treatment and a generally deficient sense of urgency. [64-66]

Two other essential characteristics of successful MoCs that Bruggmann and Litwin emphasised in their MoC study, [17] a multidisciplinary approach and integration of services, are addressed below in the sections responding to the questions of who and how, respectively.

Where

The delivery of HCV services and interventions varies tremendously in practice. Table 3 identifies the diverse settings where they can be offered. This section and the next draw on the scientific literature for recent experiences in implementing MoCs for HCV, especially among PWID, to explore the questions of where, what, who and how.

Because MoCs are setting-dependent, we have devoted particular attention to the question of where. The rest of this section is devoted to the different settings that can provide the primary venue for HCV services. While a “one-stop shop” may be ideal, in that it provides continuity, it can be difficult to arrange financing for an integrated clinic offering a variety of health and social services in a system where funding comes from narrowly defined budgets. Moreover, clients often access services according to convenience, and providing services at a variety of sites may offer welcome flexibility. In such cases, it is critical to coordinate service provision so that clients receive consistent, seamless care regardless of location.

Where to provide the services: hospitals. For decades, hepatitis C has been managed as a rule by specialists in hospitals.[17, 39] As evidence became available on the effectiveness of HCV treatment and the need for tailored care pathways, new MoCs were developed. A systematic review of

interferon-based treatment for PWID [67] found satisfactory results in the six studies analysing SVR and in the five analysing reinfection.[68-70] While there appeared to be no clear advantage in providing treatment to PWID in hospitals instead of community-based settings, [67] most of the studies comparing HCV treatment in tertiary/specialist settings with community settings in another systematic review showed generally better uptake in the latter. [71] The main challenge is thus simplifying care at integrated centres and limiting the hospital role in HCV treatment. While hospital specialists may continue to play a key role in integrated HCV care for marginalised populations, hospital referrals should ideally be necessary only in cases with severe complications, such as advanced liver disease and certain co-morbidities (which are expected to become much less common as DAA therapy becomes more widespread). First, however, restrictions on DAA treatment in nonhospital settings [72] must be lifted to make such a shift possible.

Primary care facilities. The feasibility of successfully treating PWID receiving OST with interferon-based regimens has been broadly demonstrated in studies where well-trained general practitioners work with nurses, social workers and other professionals in a primary care setting.[73-75] This model can also benefit from telehealth technology.[76]

The experience of Kirketon Road Clinic [77] in Sydney sheds light on the benefits of delivering DAA therapy in primary care (Table 1, Case 1). Among 242 marginalised PWID who started DAA therapy, overall 68% achieved SVR by week 12 and only 2 documented virological failures were observed, per protocol SVR12 was therefore 99%, with the remainder not attending for an SVR12 test. Seventy-nine of these people received enhanced support in the form of daily or weekly administration of DAAs. Homelessness was associated with requiring enhanced support, but reassuringly this approach ensured that virological outcomes and adherence were high. Further research is warranted on the impact of housing services on long-term outcomes for PWID.[78-79]

Multidisciplinary primary care facilities in the United States that provide training and support to professional staff have been found to provide high-quality assessment and treatment of PWID with HCV,[80-82] but they are not yet common. [83] It is unclear if shifting from an MoC relying on infectious disease doctors working in primary care settings to an integrated-care pathway led by general practitioners or nurse-practitioners can be both effective and cost-effective. General practitioners are still prohibited from prescribing DAAs in most countries, [3] or are limited to delegated prescribing, but in countries where they may prescribe freely, such as Australia, the proportion of DAAs they prescribe is high.[84]

Community health centres. These community-based facilities are not fully integrated into the healthcare system. The term is used here for centres whose primary focus is *not* drug addiction. There are several examples of community health centre MoCs from the interferon era [71]. In 2001–2005, the overall SVR for a Canadian treatment cohort, most of them PWID, was 61%, which was comparable to outcomes from contemporaneous randomised controlled trials.[85]

In one systematic review of community-based HCV treatment, most studies were undertaken at OST facilities, but none assessed DAA delivery in the community setting.[71] Studies in Toronto [86] and Philadelphia [87] (Table 1, Cases 2 and 3**)** provide evidence of the effectiveness of community-based MoCs involving OST and DAAs, and a project in Brighton shows promising preliminary results. [88] A Melbourne trial is comparing a control group treated with DAAs and followed at the tertiary level with an intervention group treated and followed at community health centres. [89]

Addiction centres and harm reduction centres. Addiction centres include drug addiction treatment centres, primary addiction care units and facilities providing services to help PWID cope with medical and psychological issues related to addiction. Harm reduction centres include OST facilities, NSPs and supervised injecting centres; many incorporate peer-based services with medical support.

A Danish project has provided important evidence of DAA therapy being used in addiction centres affiliated with hospital infectious disease departments. Preliminary results show that PWID can be tested and treated outside of hospitals, using specialists who prescribe DAAs without ever seeing the patient in person (Table 1, Case 4). [90] In an East London study, 83 of the PWID attending an outreach clinic, where a consultant hepatologist and a nurse reviewed client cases, expressed interest in receiving antiviral therapy, and 58 completed treatment. Compliance was greater than 80%; homelessness, active drug injection and pre-treatment antidepressant therapy were *not* associated with noncompliance. [91]

In an Australian multicentre initiative known as ETHOS, 24% of 415 PWID were treated with interferon-based regimes; of them, 62% were receiving OST. Among the treated PWID, adherence was 86% and SVR 74%.[92] Studies of OST cohorts in Norway [93] and Ireland [37] show similarly encouraging results. Such figures are expected to improve even more as the use of DAAs becomes universal.

Scant data are available from recent studies using DAAs in OST settings, [94] though an international trial from 2016 concluded that drug use ought not to be a barrier to DAA therapy in patients receiving opioid agonist therapy. [95] Further, acceptability and feasibility of dosing DAAs through an OST infrastructure has been demonstrated. [96]

NSPs too have been shown to be effective and cost-effective in preventing both HIV [97] and HCV transmission among PWID. [98-99] They are essential for optimising linkage to care and testing, especially among young PWID,[100] and can also serve as a venue for HCV treatment. A large Australian study of PWID attending NSPs in 1999–2011 found that the proportion treated for HCV increased over time, although overall numbers never exceeded 10%. [101]

There is also evidence for the effectiveness of supervised injecting centres in preventing HCV and other blood-borne infections and avoiding other serious medical complications. [102-103] Assessment for liver disease has proven suitable in this setting. [104-105] However, beyond a survey of hepatitis C services offered at supervised injecting centres globally, [106] we found no studies assessing implementation of HCV treatment pathways through such centres. Moreover, models involving these centres, such as the “service model” used by the European Monitoring Centre for Drugs and Drug Addiction, rarely address HCV.[107] Basic work is thus still needed to conceptualise the role of supervised injecting centres within the HCV cascade.

Prisons. PWID, both former and current, form a large proportion of the prison population. [108] A study involving 3126 HCV-infected individuals incarcerated in the United States showed that rates of linkage to care and treatment for adults were very low, with just 18% being evaluated for initiation of treatment while incarcerated, and a mere 10% initiating DAAs. [109] The high burden of HCV infection in prisons, together with the presence of other conditions such as HIV infection, HBV infection or drug use, creates a syndemic cluster that is difficult to address. On the other hand, surveillance and movement restrictions allow for straightforward implementation of diagnostic and

therapeutic strategies. For instance, a recent modelling study concluded that incarceration contributes a 28% risk of HCV transmission among PWID in Scotland, but scaling up HCV treatment to 80% of chronically infected PWID with sufficiently long sentences (>16 weeks) upon entrance to prison was able to reduce both the incidence and prevalence of HCV by 46%.[110] Offering prisoners HCV services upon intake is quite rare, however. Another recent study using a prevention benefit analysis concluded that increasing HCV testing in United Kingdom prisons is marginally cost-effective compared to current voluntary risk-based testing, but it could be highly cost-effective if DAAs are broadly prescribed and PWID treatment rates increased.[111] A similar United States study drew similar conclusions. [112] Other authors have demonstrated that scaling up harm reduction services is a prerequisite to effectively tackling HCV, HIV and drug epidemics in prisons.[113] Another challenge is ensuring prisoners uninterrupted treatment upon release. One study offered prisoners who began DAA therapy while in prison but who were released early with their remaining medication to complete treatment in the community. [114] This same study also offered short sentence duration prisoners ineligible for treatment referrals to healthcare services for treatment in the community once released.

A systematic review of the effectiveness of MoCs for HCV in European prisons found that seven studies utilising second-generation DAAs in France, Italy and Spain achieved SVR rates of 85% to 98%, and one study that switched from interferon therapy to DAA therapy increased SVR rates from 62%–68% to 90%–98%. [115] A Spanish study demonstrated that HCV elimination is possible in a prison setting. Using a test-and-treat strategy, the prison tested 99.5% of its inmates, treated all who were infected and would be incarcerated more than 30 days, established a teleconsultation programme for those who were released, and achieved SVR in 97% of the treated prisoners (Table 1, Case 5)**.** [116]

Pharmacies. Available evidence supports including pharmacies as essential service venues in MoCs for treating HCV in PWID (Table 1, Case 6). [36,117] Some pharmacies dispense OST and thus have daily contact with people on OST, and some also offer needle and syringe services. One study demonstrated the feasibility of implementing DAAs through a community pharmacy for PWID receiving OST. [36]

In addition, both rapid testing using dried blood spots [118] and syringe distribution [119] have been proven effective in community pharmacies. These findings suggest that any further development of MoC designs and policies to incorporate HCV services for PWID at pharmacies should be based on the use of standard community pharmacies rather than hospital or specialist pharmacies, which can pose barriers to PWID access.

Sexual health clinics. Sexual health clinics provide a good platform for linkage to the HCV cascade. Australian and United Kingdom studies have demonstrated that interferon-based treatment in sexual health clinics, including follow-up and regular assessments, resulted in SVRs comparable to treatment at specialist clinics. [120-122] However, we were unable to identify any studies assessing rapid point-of-care testing followed by DAA therapy in this setting. Other studies from Australia and the United Kingdom linking confirmed HCV infections in sexual health clinics to injecting drug use have shown that HCV and HIV screening is feasible there but probably insufficient. [1423-124] It has not yet been determined whether HCV screening in this setting should be clinician-led, as with these studies (which showed an HCV incidence of around 3%), or whether universal routine HCV testing

should be implemented there instead. Guidelines on who to test for hepatitis C in sexual health services are available, and often risk-factor based [125]. In either case, in order to achieve elimination in high-risk populations such as men who have sex with men, primary prevention and the prevention of reinfection will play a major role. [126-128]

What, who, and how

What services to provide. It is well worth consulting the latest HCV guidelines from WHO, [129-130] the European Association for the Study of the Liver (EASL), [34] the American Association for the Study of Liver Diseases (AASLD), [131-132] and the International Network on Hepatitis in Substance Users [133]. These guidelines all include concrete recommendations for providing HCV services to marginalised populations, and the WHO guidelines specifically address the needs of low- and middle-income countries. In addition, several systematic reviews helpfully provide an overview of the evidence for various interventions for PWID in the DAA era.[23-24, 134-135]

Simplicity, scalability and patient convenience should be the bywords in developing an MoC. They call for a test-and-treat model wherever possible, to eliminate the gaps between testing and treatment.[136-143] Strong referral links in all directions between testing, treatment, harm reduction and social services are of paramount importance. In countries with high diagnosis rates, attention should be paid to reengaging PWID who have been diagnosed in the past and getting them into care. For a high-prevalence population like PWID, rapid antigen or RNA testing is appropriate, the latter providing results within an hour, [137, 144-145] and it may be sensible to omit genotyping if there is no major price differential between pangenotypic DAAs and genotype-specific ones. If transient elastography is not readily available, it may make sense to skip or postpone it too, or use alternative easily available fibrosis assessment tools such as APRI [146]. Table 4 summarises the findings from the literature search organised by the stages in the cascade of care.

DAA therapy is now the treatment of choice for all patients and everything should be done to ensure its availability. [35, 147] Access to harm reduction services are critical, as discussed above, to reach key, high-burden populations. Finally, good patient follow-up and contact are essential to help ensure adherence and maximise cure rates. Appropriate peer support, as discussed in the next section, can be crucial in increasing service uptake and retention, particularly in working with marginalised populations.

Who to provide the services. Throughout the HCV cascade of care, multidisciplinary teams of healthcare and social service professionals can help ensure the best possible outcomes, which in turn will improve public health. That is why the International Network on Hepatitis in Substance Users recommends treating HCV in a multidisciplinary team setting. [148] Multidisciplinary approaches encompassing biomedical, psychoeducational and social interventions have been shown to improve engagement in care, [149] treatment uptake, [149-151] patient adherence and retention, [152-157] management of HCV/HIV coinfection [158] and of HCV in psychiatric patients,[159] stigma reduction and patient well-being,[28, 87] and reduction in mortality.[141] However, the creation of multidisciplinary teams or structures where existing structures are functioning effectively is not a requirement of a good MoC.

As mentioned above, in moving from MoCs designed around interferon-based treatment to MoCs designed around DAAs, HCV services should be provided in a variety of settings to facilitate scale-up.

With DAA therapy, HCV assessment and treatment no longer require specialist training, so it makes sense to expand who may assess HCV infection and prescribe treatment beyond specialists in tertiary care centres. With proper training, anyone can undertake assessment and prescribe DAAs competently, either as a delegated prescriber or a nonmedical prescriber – which again facilitates scale-up. Evidence has shown good results from the prescribing of DAAs by primary care providers, drug and alcohol service providers, nurse-practitioners, nurses, including nurse prescribers, and pharmacists.[160-163] Delegated prescribing may be a good option where prescribing is limited by statute. Table 5 presents the diversity of providers featured in the 71 recent MoC studies reviewed for this paper, including 18 studies highlighting the benefits of multidisciplinary teams.

Particularly when using non-specialist service providers, it is essential to invest in human resources, hiring the best people for the job and providing them with thorough and regular training. One model that has proven useful in helping such providers serve vulnerable and dispersed populations is the model promoted by Project ECHO (Extension for Community Healthcare Outcomes).[164] By engaging frontline service providers with a continuous learning system and specialist mentors, it can dramatically increase the access of PWID to HCV care and treatment. [165-166]

A peer provider can use shared experience, as someone who has had chronic hepatitis C and/or someone who has been part of a target population, to connect with vulnerable people and help them through the cascade of care. They can also use their experience to help ensure that MoCs reflect client concerns. Limited data from both the interferon era [167] and the DAA era highlight [168-169] the potential benefit of including peer support workers in MoCs.

Countries with very broad community access to DAAs, such as Australia, [170] have been successful in mobilizing the peer workforce and training them to provide services at different points in the cascade of care, where they have been crucial in building momentum towards HCV elimination.

How to integrate services. In the DAA era, as mentioned above, the ideal form for a successful MoC for PWID with HCV is either a one-stop-shop approach, in which all relevant services are integrated in locations where people are already accessing other services, or a flexible approach, in which various sites and services are well coordinated and strongly linked. The challenge in implementing the one-stop approach is to evolve towards comprehensive yet decentralised points of care, [171] for instance through single-visit diagnoses.[137] Multidisciplinarity and integration go hand in hand, yet it is important to emphasise two necessary features of the integration process in developing a robust MoC for marginalised populations. First, integration should take place within systems where these populations already access services, particularly OST and NSPs in the case of PWID. [172] The aim should be to bring services closer to the client, rather than expecting the client to seek them out. And second, it requires training that is also multidisciplinary and integrated, which will include task-shifting, so that fewer kinds of professionals are providing more services in the same settings, thereby necessitating fewer visits to access them.

In their seminal review on MoCs for HCV, Bruggmann and Litwin contrast various integrated MoCs with conventional secondary and tertiary care models. [17] Where it is feasible and affordable, we advocate integration: delivering integrated care in non-specialist settings that are better suited to the care of vulnerable individuals. In Scotland, where managed care networks exemplify integrated multiagency MoCs, they have been shown to improve not only HCV outcomes, but also outcomes related to drug use. [141, 173-174]

Although not exhaustive, we have presented many examples demonstrating that integrated MoCs are effective in addressing the entire HCV cascade of care (Fig. 1), plus evidence that an integrated format might be particularly well suited to primary care, community health centres, addiction and harm reduction centres, prisons, sexual health clinics, pharmacies and other settings. Such models of care can target both the typical young drug user and the veteran of addiction treatment, [175-176] for instance, thereby increasing overall eligibility for HCV treatment [177] while providing for appropriate counselling, peer support [149] and management of medical, mental health and social issues for both those on opioid substitution therapy and those who are not.[75, 88, 178-179]

Conclusion

Around the world, models of care for HCV need to be redesigned to reflect the recent availability of DAAs if countries are to meet their commitments to eliminating HCV as a public health threat by 2030, as set out by WHO. In some countries, this will require major changes to established care pathways and systems. One immediate challenge for policymakers and researchers is to develop cost-effective, easily implemented mechanisms that incorporate health information and reimbursement systems, and interdisciplinary and multifacility communication. Healthcare providers, affected populations and other key stakeholders should be involved in such development to ensure that the final mechanisms represent relevant perspectives and are mutually beneficial to all. While further research on the feasibility of different MoCs in specific settings is needed, much can be learned from examining the innovative MoCs reviewed here, which suggest that an effective model of care for HCV infection should be simple, targeted, multidisciplinary, scalable, integrated, patient-centred and affordable.

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Table 1. Models of Care for Hepatitis C in People who Inject Drugs – some representative cases

Study, project, and location	**Where** (setting)	**What** (services)	**Who** (providers)	**How** (integration approach)	**Findings**
1. Read et al., 2019[1] Kirketon Road Centre (KRC), Sydney, Australia	Primary health care facility targeting PWID, sex workers and "at-risk" young people	Viral hepatitis testing, DAA therapy, hepatitis A and B vaccination, "healthy liver clinic" with specialized hepatitis service; sexual health services; drug and alcohol counselling, assessment and referrals; crisis intervention; housing, social service and welfare assistance; methadone access and case management; NSP; street van and bus outreach; HIV testing and counselling; general health services	GPs, nurses, social workers	Integrated primary health care model offering anonymous services to risk populations. DAAs can be provided through a community pharmacy, with a follow-up phone call to confirm treatment initiation, standard of care pathology. Enhanced adherence support includes phone calls or other contact at least weekly, flexible directly observed dispensing of the medications, with or without OST, linkage to partner organisations, DAA delivery to prisons, police cells, psychiatric units and general hospital wards.	242 PWID were included, 74% recent or current injectors, 44% enrolled in OST. 79 (32%) of clients chose enhanced daily or weekly dosing support options. Enhanced support was associated with homelessness, daily injecting, Aboriginality, mental health co-morbidity and poly-drug use (all $p<0.001$). Overall adherence was 86%, and 92% of patients missed one or more doses (median 10, IQR 4-24). The study confirms that PWID can be successfully treated for HCV in a real-world setting using an integrated primary health care model and demonstrates the feasibility of scaling DAA therapy up in high-risk PWID populations.
2. Mason et al., 2017[2]	A partnership between three community	Treatment assessment, DAA therapy, weekly pre- and post-treatment	Nurses, nurse-practitioners,	Integrated multidisciplinary specialist support on site	74 PWID initiated DAA therapy, achieving high adherence and SVR with appropriate support. Participants housing status and

[1] Read P, Gilliver R, Kearley J, Lothian R, Cunningham E, Chronister K, Dore G. Treatment Adherence and Support for People who Inject Drugs Taking Direct Acting Antiviral Therapy for Hepatitis C Infection. Journal of Viral Hepatitis. 2019. Accepted.. In press

[2] Mason K, Dodd Z, Sockalingam S, Altenberg J, Meaney C, Millson P, Powis J. Beyond viral response: a prospective evaluation of a community-based, multi-disciplinary, peer-driven model of HCV treatment and support. Int J Drug Policy. 2015 Oct;26(10):1007-13.

Toronto Community Hep C Program (TCHCP), Toronto, Canada	health centres to provide underserved populations with low-threshold access to HCV care	questionnaires, follow-up	family physicians		income increased significantly during the study.
3. Trooskin et al. 2015[3] Do One Thing, Philadelphia, United States	Community-based program in a medically underserved neighbourhood with high rates of HCV and HIV	Social marketing campaign, door-to-door outreach, rapid HIV and HCV screening in a mobile medical unit, immediate phlebotomy for confirmatory testing of reactive antibody tests, facilitation of client enrolment in health insurance, linkage to care and retention in care	Trained HCV test counsellors, phlebotomists, patient navigators, social workers; linkage to primary care physicians and HCV subspecialists	Developed and coordinated a local hospital and local university	Among 1301 people screened, 2.8% were chronically infected, half of whom were newly diagnosed. The biggest barrier to retention in care was obtaining referrals for subspecialty providers due to a lack of insurance. Some subjects started treatment, while many who were eligible were awaiting approval from insurance companies. This study illustrates how a good model of care can adapt to local circumstances.
4. SACC, 2017;[4] **Linnet et**	12 drug counselling	Hepatitis and HIV counselling and testing;	GPs, hospital specialists,	Decentralised shared care model, in which hospital infectious disease	More than 700 people were screened for viral hepatitis and HIV. The proportion of

[3] Trooskin SB, Poceta J, Towey CM, Yolken A, Rose JS, Luqman NL, Preston TW, Chan PA, Beckwith C, Feller SC, Lee H, Nunn AS. Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. J Gen Intern Med. 2015 Jul;30(7):950-7. doi: 10.1007/s11606-015-3209-6. Epub 2015 Feb 14.

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al., 2017[5] Shared Addiction Care Copenhagen (SACC) Project, Copenhagen, Denmark	and treatment centres; 1 hospital infectious disease department	transient elastography, DAA therapy, management, follow-up; various drug and alcohol treatment and harm reduction services	social service providers	department was responsible for prescription and monitoring the course of treatment, while the drug treatment staff were responsible for testing, assessment, dispensing and adherence support	clients tested for HCV in the treatment centres increased by 50%, and 208 were diagnosed with chronic HCV infection; 25 of them ended up being treated and cured. The model permitted many more people to be diagnosed and cured than otherwise, despite little tradition of collaboration between the centres and the hospital.
5. Cuadrado et al., 2018[6] El Dueso Prison, Santoña, Cantabria, Spain	Prison healthcare facility	HBV, HCV and HIV screening and diagnosis; DAA therapy, teleconsultation; phylogenetic analysis of nonresponders, followed by targeted retreatment	Prison health team (physicians, nurses, pharmacist); addiction specialists; social service providers; hospital team (infectious disease specialists, hepatologists, specialized nurses, radiologists, ID specialists, pharmacists,	A video collaboration tool was used for consultations between prison and hospital teams, as well as between treatment recipients and a hospital hepatologist, also after any inmate release. Treatment was prescribed by the hepatologist and administered by the prison healthcare providers. Prisoners were consulted on study design, and their input contributed to the use of telemedicine and the choice of the quickest treatment regiment (non-ribavirin).	A test-and-treat strategy enabled the prison to screen 99.5% of its inmates for HCV, treated everyone who was infected and would be in prison more than 30 days, established a teleconsultation programme for those who were released. The programme achieved SVR in 97% of the treated prisoners. At the end of the programme, no inmate had any detectable HCV RNA.

[5] Linnet M, Peters L, Raben d, Petersen H, Gerstoft J, Lundgren J. Organizational barriers as an explanation for differences in offer and uptake rates for hepatitis A/B/C and HIV testing in three drug treatment centres in Copenhagen. Poster presented at HepHIV 2017; 2017; Malta. http://www.hiveurope.eu/Portals/0/Conference%202017/Posters/PS1_03.pdf.

[6] Cuadrado A, Llerena S, Cobo C, Pallas JR, Mateo M, Cabezas J, et al. Microenvironment eradication of hepatitis C: a novel treatment paradigm. Am J Gastroenterol. 2018 Nov;113(11):1639–1648.

			psychologists); telemedicine expert		
6. Radley et al., 2017[7] Directly Observed Therapy for Hepatitis C (DOT-C), Dundee, Scotland, United Kingdom	Community pharmacies	Dried blood spot testing, OST, DAA therapy	Pharmacists, physicians	Community pharmacies referring patients who test positive for HCV to clinics for assessment and treatment	HCV testing and treatment is feasible in community pharmacies, especially for patients already receiving OST there. Compared to nurse-practitioners, pharmacists were much more likely to get patients to take a rapid HCV test, and for clients with reactive tests, the pharmacist were much more successful in getting them to attend a clinic for assessment and treatment.
7. Hashim A et al[8] VALID (vulnerable adults liver disease) Study, Southeast England, UK	Hostels, Community clinics	Point of care testing, liver fibrosis assessment (Fibroscan), alcohol and substance misuse counseling/ social support (provided by primary care physician) and HCV treatment. A specialist registrar runs the clinics under	General practitioner, medical specialist	One stop HCV clinic at two major homeless hostels in Southeast England.	72 attended the clinic, 71 (99%) were included in the program, 28 (39,4%) were anti-HCV positive, 26/28 consented to further testing, 20/26 were HCV RNA positive, 5/20 started DAA treatment. Results in 2019: 131 individuals approached, 127/131 individuals enrolled in the program, 59/127 were HCV Ab positive, 48/59 were HCV RNA posiitve, 28/48 initiated HCV treatment, 14/17 achieved SVR12, 13 still on

[7] Radley A, Tait J, Dillon JF. DOT-C: a cluster randomised feasibility trial evaluating directly observed anti-HCV therapy in a population receiving opioid substitute therapy from community pharmacy. Int J Drug Policy. 2017 Sep;47:126-136.

[8] Hashim A et al. Hostel-based models can improve the engagement of homeless individuals with liver services: VALID (vulnerable adults liver disease) study. EASL ILC 2019.

		the supervision of a Hepatologist.			treatment/waiting SVR results, 1 discontinued the treatment.
8. **Shiha G et al.** [9] HCV elimination in general population, Egypt	Rural setting	Point-of-care testing, liver fibrosis assessment, complete laboratory work, treatment initiation with DAAs	Multidisciplinary	Awareness raising campaign followed by HCV screening by using HCV antibody RDT a week later. Anti-HCV positive got tested for HCV RNA with GeneXpert IV, and on the same day the HCV RNA positive patients had the Fibroscan, abdominal ultrasound and basic laboratory work (liver function, renal function, CBC, AFP) and initiated treatment with DAA.	475 individuals were screened for anti-HCV antibodies by RDT, 56 had PCR HCV RNA, 43 positive for HCV RNA, 40 initiated the treatment, 3 were excluded due to focal hepatic lesion and pregnancy.

[9] Shiha G, et al. Towards HCV elimination: Feasibility of complete linkage to care by testing and treatment on the same day of screening: A pilot study. EASL ILC 2019.

Table 2. Populations addressed in the models of care selected

Population (n)	Country	N. of study (from Supplementary material 1)
PWUD*/ on OST *(42/3)*	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Ireland; Norway; Portugal; Spain; Switzerland; UK; USA	Papaluca T et al. (1), Alimohammadi A et al. (2), Remy AJ et al. (3), Bourgeois S et al. (4), Chronister KJ et al. (6), Valencia JA et al. (7), Liberal R et al. (8), Inglis SK et al. (10), Ford MM et al. (11), Borojevic M et al. (12), Peters L. (13), Williams B et al. (14), Saludes V et al. (15), O'Loan J et al. (16), Grebely J et al. (17), Norton et al. (30), Morris et al. (31), Schulkind J et al. (33), Saludes V et al. (34), Radley A et al. (35), Alam Z et al. (37), Sypsa V et al. (40), Kugelmas M et al. (42), Howell et al. (43), Kraichette N et al. (44), Greenan S et al. (45), Ryder N et al. (46), Doyle J et al. (47), Bielen R et al. (48), Stvilia K et al. (49), Mitchell S et al. (50), Thompson H et al. (51), Lamond S et al. (53), Sinan F et al. (54),Midgard H et al. (56), Berger SN et al. (57), Read P et al (60), Mason K et al (62), Hashim A et al (63), Treloar C et al (64), Chronister KJ et al (65), Linnet et al (65), Barror S et al. (66), Simoes D et al. (68), Nouch S et al (69), Scherer ML et al. (71) **Specifically OST**: Inglis SK et al. (10), Radley A et al. (35), Bielen R et al. (48)
General population *(20)*	Australia; Canada, Egypt; India; Mexico; Pakistan; USA	Balcomb A (5), Ford MM et al. (11), Trooskin et al. (18), Chiong F et al. (23), Cooper et al. (24), Capileno et al. (25), El-Akel et al. (26), Kattakuzhy et al. (29), Dhiman RK et al. (36), Shiha G et al. (38), Shiha G et al. (39), Greenan S et al. (45), Ryder N et al. (46), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55), Koren D et al. (59), Sokol et al (61), Nouch S et al (69)
Prisoners *(11)*	Australia; France; Ireland; Portugal; Romania; Spain; Sweden; UK	Papaluca T et al. (1), Remy AJ et al. (3), Liberal R et al (8), Cuadrado A et al (9), Inglis SK et al. (10), Vroling H et al. (20), Olsson A et al. (21), Bartlett SR et al. (22), Overton et al. (41), Barror S et al. (66), McDonald L et al. (70)
Homeless *(7)*	Australia; Canada, France; Romania; Scotland; Spain; UK	Alimohammadi A et al. (2), Remy AJ et al. (3), O'Loan J et al. (16), Grebely J et al. (17), Hashim A et al. (28), Macbeth K et al. (32), Barror S et al. (66)
Sex workers *(5)*	Australia; Ireland; Italy; Romania; Spain; Portugal; UK	Chronister KJ et al. (6), Read P et al. (60), Barror S et al. (66), Teti E et at. (67), Simoes D et al. (68)
Migrants	France, Portugal	Remy AJ et al. (3), Saludes V etl al. (34), Simoes D et al. (68)

(3)		
People with mental health issues *(2)*	Canada, France	Mason K et al (62), Remy AJ et al. (2)
Other (reviews) *(2)*	Multi-country reviews	Pourmarzi et al. (19), Wade et al. (27)
Veterans *(1)*	USA	Fleming BS et al. (58)
MSM *(1)*	Portugal	Simoes D et al. (68)

* People who use drugs

Table 3. Setting in the models of care selected

Setting (n)	Country	N. of study (from Supplementary material 1)
Low-threshold setting *(25)*	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Italy; Ireland; Norway; Portugal; Romania; Spain; UK; USA	Alimohammadi A et al. (2), Remy AJ et al. (3), Bourgeois S et al (4), Valencia JA et al. (7), Ford MM et al. (11), Williams B et al. (14), Saludes V et al (15), O'Loan J et al. (16), Grebely J et al. (17), Hashim A et al. (28), Morris et al. (31), Schulkind J et al. (33), Saludes V et al. (34), Sypsa V et al. (40), Howell et al. (43), Stvilia K et al. (49), Mitchell S et al. (50), Sinan F et al. (54), Midgard H et al. (56), Treloar C et al (64), Chronister KJ et al (65), Linnet et al (65), Barror S et al. (66), Teti E et al. (67), Simoes D et al. (69), Scherer ML et al. (72)
Primary care *(20)*	Australia, Canada, Ireland, Mexico, Pakistan, Romania, Scotland, Spain, UK, USA	Balcomb A (5), Chronister KJ et al. (6), Trooskin et al. (18) Capileno et al.(25), Kattakuzhy et al.(29), Norton et al. (30), Macbeth K et al. (32), Doyle J et al. (47), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55), Koren D et al. (59), Read P et al (60), Sokol et al (61), Mason K et al (62), Hashim A et al (63), Treloar C et al (64), Chronister KJ et al (65), Barror S et al. (66), Nouch S et al. (69)
Prison *(9)*	Australia, Ireland, Romania, Spain, Sweden, Portugal, UK	Papaluca T et al. (1), Liberal R et al (8), Cuadrado A et al (9), Vroling H et al. (20), Olsson A et al. (21), Bartlett SR et al. (22), Overton et al. (41), Barror S et al. (66), McDonald L et al. (70)
High-threshold setting *(6)*	Belgium, Denmark, Switzerland, USA	Borojevic M et al (12), Peters L. (13), Alam Z et al. (37), Kugelmas M et al. (42), Bielen R et al. (48), Berger SN et al. (57)
Hospital *(4)*	Australia, Canada, India	Chiong F et al. (23), Cooper et al. (24), Dhiman RK et al. (36), Ryder N et al. (46)
Rural *(4)*	Canada, Egypt, France	Cooper et al. (24), Shiha G et al. (38), Shiha G et al. (39), Kraichette N et al. (44)
Regional setting *(3)*	Canada, Egypt, UK	Inglis SK et al. (10), El-Akel et al. (26), Greenan S et al. (45)

Pharmacy *(3)*	Scotland, USA	Radley A et al. (35), Fleming BS et al. (58), Koren D et al. (59)
Mobile van *(4)*	Australia, France, USA	Remy et al. (3), Trooskin S et al. (18), Kraichette N et al. (44), Doyle J et al (47)
Other *(2)*	Multi-country reviews	Pourmarzi et al. (19), Wade et al. (27)

Table 4. Providers in the models of care selected

Providers (n)	Country	N. of study (from Supplementary material 1)
Multidisciplinary* *(22)*	Australia; Canada; Denmark; Egypt; France; Greece; Ireland; Portugal; Romania; Spain; Switzerland; UK; USA	Alimohammadi A et al. (2) Remy et al. (3), Balcomb A (5), Chronister KJ et al. (6), Valencia JA et al. (7), Cuadrado A et al (9), Inglis SK et al. (10), Ford MM et al. (11), Borojevic M et al (12), Peters L. (13), Trooskin S et al. (18), El-Akel et al. (26), Morris et al. (31), Macbeth K et al. (32), Shiha G et al. (39), Sypsa V et al. (40), Fleming BS et al. (58), Mason K et al (62), Chronister KJ et al (64), Linnet et al (66), Barror S et al. (66), Simoes D et al. (68)
Medical specialists^ *(26)*	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	Papaluca T et al. (1), Alimohammadi A et al. (2), Bourgeois S et al (4), Liberal R et al (8), Williams B et al. (14), Olsson A et al. (21), Bartlett SR et al. (22), Chiong F et al. (23), Hashim A et al. (28), Kattakuzhy et al. (29), Norton et al. (30), Dhiman RK et al. (36), Alam Z et al. (37), Overton et al. (41), Kraichette N et al. (44), Greenan S et al. (45), Ryder N et al. (46), Mitchell S et al. (50), Thompson H et al. (51), Lamond S et al. (53), Midgard H et al. (56), Berger SN et al. (57), Sokol et al (61), Hashim A et al (63), McDonald L et al. (70), Scherer ML et al. (71)
General practitioners *(12)*	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	O'Loan J et al. (16), Chiong F et al. (23), Hashim A et al. (28), Kattakuzhy et al. (29), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55)*, Sokol et al (61), Mason K et al (62), Barror S et al. (66), Nouch S et al. (69) **Defined in manuscript as "doctors without speciality training"*
Telemedicine *(7)*	Australia; Spain; Canada; Mexico; USA	Balcomb A (5), Cuadrado A et al (9), Vroling H et al. (20), Olsson A et al. (21), Cooper et al. (24), Perez Hernandez JL et al. (52), Komaromy M et al (67)
Nurse-led *(14)*	Australia; Belgium; Canada; Georgia; Sweden; UK; USA	Papaluca T et al. (1), Williams B et al. (14), Vroling H et al. (20), Olsson A et al. (21), Kattakuzhy et al. (29), Schulkind J et al. (33), Doyle J et al. (47), Bielen R et al. (48), Stvilia K et al. (49), Mitchell S et al. (50), Sinan F et al. (54), Berger SN et al. (57), Hashim A et al (63),McDonald L et al. (70)
Specialist nurse (but not nurse-led) *(12)*	Australia; Belgium; Canada; Norway; UK; USA	Bourgeois S et al (4), O'Loan J et al. (16), Bartlett SR et al. (22), Chiong F et al. (23), Cooper et al. (24), Radley A et al (35), Overton et al. (41), Greenan S et al. (45), Thompson H et al. (51), Naveed A et al. (55) Midgard H et al. (56), Fleming BS et al. (58)
Peer-support (3)	Australia; Belgium	Bourgeois S et al (4), Chronister KJ et al (6), Treloar C et al (64)
Pharmacists	Pakistan; UK; USA	Radley A et al. (35), Fleming BS et al. (58), Koren D et al. (59)

(3)		
Non-governmental organization *(1)*	Pakistan	Capileno et al. (25)
Not reported/Not specified *(8)*	Australia; Egypt; Spain; USA	Saludes V et al (15), Grebely J et al. (17), Saludes V et al. 2 (34), Shiha G et al. (38), Kugelmas M et al. (42), Howell et al. (43), Read P et al (60), Teti E et al. (67)
Other (reviews) (3)	Multi-country reviews	Pourmarzi et al. (19), Vroling H et al. (20) Wade et al. (27)

*A multidisciplinary team was defined as including non-clinical key personnel on the team in addition to clinicians (i.e. social worker, case manager, psychologist, etc.)

^A medical specialist was defined as any medical doctor that had speciality training such as; hepatologists, gastroenterologists, infectious disease specialists, sexual health physicians, HCV clinicians)